REMARKS

Claims 1-5 are pending.

Interview Request

Applicants' representative, Garth M. Dahlen, Ph.D., Esq. (#43,575) has attempted to contact Examiner Habte to schedule an Interview. Unfortunately, Examiner Habte is on vacation until July 28, 2006. Dr. Dahlen respectfully requests that Examiner Habte contacts Dr. Dahlen upon Examiner Habte's return from vacation to schedule a personal Interview to discuss the outstanding issues.

Issues under 35 U.S.C. 102(b)

The Examiner has maintained the rejection of claims 1-5 under 35 U.S.C. 102(b) as being anticipated by Kaspersen et al. (Journal of Label. Comp. and Radiopharm., Vol. 27, No. 9, 1055, 1989). Applicants respectfully traverse the rejection.

The Examiner has maintained the position that Applicants are required to repeat the experiments of Kaspersen et al. to show that the mirtazapine crystals of Kaspersen et al. do not have (i) a water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours, as presently claimed. *Applicants respectfully submit that Applicants have repeated the experiments of Kaspersen et al. to the extent that it is possible.*

The Examiner does not appear to understand that the exact conditions for drying the crystals are not taught by Kaspersen et al. As such, Applicants are left to make an educated guess at the drying conditions which were used by Kaspersen et al.

In the next communication from the Examiner (which may be done orally in the personal Interview), Applicants respectfully request that the Examiner describes the exact drying

conditions which Applicants should use to exactly repeat the crystal workup of Kaspersen et al. Applicants are very receptive to understanding what the Examiner believes are the drying conditions used by Kaspersen et al. and will seriously consider the Examiner's suggestion.

Applicants believe that given this task of trying to ascertain exactly what drying conditions should be used, the Examiner will understand Applicants' position that it is impossible to exactly reproduce this experiment of Kaspersen et al.

It is Applicants' position that Example 8 in the present specification is sufficiently close to the description of Kaspersen et al., so that the skilled artisan would come to the reasonable conclusion that the mirtazapine crystals of Kaspersen et al. do not have (i) a water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours, as presently claimed.

The workup of Kaspersen et al. is as follows:

> The product was extracted with ethyl acetate, dried over Na_2SO_4 and evaporated to dryness to yield 950 mg (85%) of crude 1c. The crude 1c was purified by chromatography over Alox B (eluted with hexane/ethyl acetate 7:3, v/v) to yield 830 mg. For the final purification the product was treated twice with 100 mg of charcoal in n-hexane (containing 1% of methanol) followed by crystallization from methanol/water (1:1, v/v) yielding 600 mg (53%) Org 3770 as colourless crystals, m.p. 123,8-125,8 °C. No impurities were detectable either on TLC, HPLC or GC.

The Examiner will note that Example 8 of the present application and the invention of Kaspersen et al. are the same in that mirtazapine is recrystallized from a solvent mixture of methanol/water.

Also, the Examiner will note that the mirtazapine of Example 8 was dried under *ordinary conditions*. It is Applicants' position that one skilled in the art would reasonably conclude that Kaspersen et al. dried the crystals under *ordinary conditions*, since they are silent on this matter. As such, it is appropriate for the Examiner to rely on the experimental data of Example 8 in the

present specification to show the properties of the final mirtazapine crystals of Kaspersen et al., and for the Examiner to rely on the experimental data of Example 7 in the present specification to show the properties of the final mirtazapine crystals of the present invention which are dried under relatively stringent conditions.

The product of Example 8 has a water content of about 3.5 % by weight, which is outside the inventive range of water content of "not more than 0.5% by weight". Since the product of Kaspersen et al. is also dried under ordinary conditions, it follows that the product of Kaspersen et al. has a water content of about 3.5 % by weight. Thus, Example 8 of the present specification is relevant to show that it is likely that the product of Kaspersen et al. is outside the inventive range of water content of "not more than 0.5% by weight".

Applicants now respond to the Examiner's comments in the February 23, 2006 Office Action.

The Examiner argues in page 5 of the outstanding Office Action that Example 8 in the present specification is not an appropriate reproduction of Kaspersen et al., since there is a pulverization step in Example 8 which is not present in the workup of Kaspersen et al.

In response, Applicants respectfully submit that in Example 8, the resulting crystals were dried under the conditions of 50°-60°C/4-5.3 kPa, to give a mirtazapine hydrate of which water content was 3.5% or less. It is also described that "The X-ray diffraction of the crystals of a mirtazapine hydrate before pulverization was examined" (at page 18, lines 18-19 of the specification), and that, as a result, it was confirmed that "the molar ratio of the mirtazapine molecules to the water molecules in the crystals was 2:1" (at page 26. lines 2-3 of the specification). Accordingly, there is no relationship between the pulverization step and the water content as the Examiner asserted at page 5 of the outstanding Office Action.

Furthermore, the pulverization step in Example 8 was carried out in order to facilitate the preparation of the mirtazapine for further drying in Example 9. However, the Examiner will note that even under the more drastic drying conditions described in Example 9, the mirtazapine still

retained more water than is instantly claimed. In Example 9, when the pulverized mirtazapine hydrate obtained in Example 8 was dried at 50°-60°C for 7 hours, the water content decreased only to 2.2%. Furthermore, it was not until the dried product was further dried under the severe conditions at the temperature of 85°-95°C for the period of 23 hours, that the water content of the crystals decreased to 0.58%. After pulverizing the resulting dried product again, the pulverized product was further dried at 85°-95°C for 6 hours, to give anhydrous mirtazapine of the present invention of which water content was 0.5% or less (*i.e.,* 0.050%). It is also described in Example 10 that the pulverized mirtazapine hydrate obtained in Example 8 was dried under the conditions of 85°-105°C/600-1333 Pa for 10 hours, to give the anhydrous mirtazapine of the present invention of which water content was 0.3%.

Accordingly, it is only in these drastic drying conditions which were not used in Kaspersen et al. that the anhydrous crystals of the instant claims were obtained.

Moreover, in page 5 of the outstanding Office Action, the Examiner asserts that "in addition, the drying process in Example 8 is also different from that of Kaspersen's." However, regarding recrystallization, Kaspersen et al. only disclose that "... followed by crystallization from methanol/water (1:1, v/v) yielding 600 mg (53%) Org 3770 as colorless crystals ..." (at page 1066, lines 5-6), but disclose no conditions of drying process. Therefore, it is reasonable to consider that the temperature condition of 50°-60°C for drying would be employed in Kaspersen et al., which was common to one skilled in the art.

Furthermore, the Examiner asserts that "Applicant's compound would be different from the prior art compound (Kaspersen) if the 'special' drying conditions when applied to the prior art compound gave a different property from what is claimed" (at page 7 of the outstanding Office Action). However, since it was the inventors of the present application who found the "special" drying conditions for the first time, the subject matter described in the instant claims is patentable over Kaspersen et al. Therefore, the Examiner's assertion is not reasonable.

Based on the foregoing, withdrawal of the rejection is respectfully requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Garth M. Dahlen, Ph.D., Esq. (Reg. No. 43,575) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Dated: July 20, 2006

Respectfully submitted,

By _____ #43595 for

Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant